

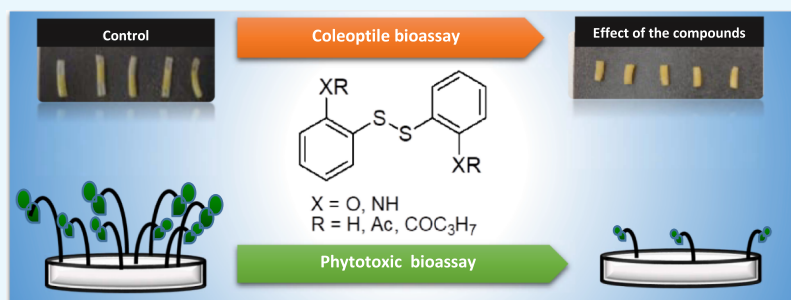
Phytotoxicity Study of Ortho-Disubstituted Disulfides and Their Acyl Derivatives

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ABSTRACT: Six different ortho-disubstituted disulfides were synthesized and evaluated in wheat coleoptiles bioassays. The most active ones were evaluated on seeds of four different plant species (*Solanum lycopersicum* L., *Lolium rigidum* Gaudin, *Echinochloa crus-galli* (L.) Beauvois, and *Urochloa decumbens* (Stapf) R. D. Webster) to evaluate their effects on the germination and plant growth, presenting, in general, higher activity than the model herbicide Logran. The results shown in this study indicate that these compounds are potential candidates as herbicide leads for weed control in agriculture.

INTRODUCTION

Organic disulfides, usually obtained by mild oxidation of thiols,^{1,2} are important compounds with interesting biological properties.³ For instance, there are many peptide drugs that contain a disulfide bond such as vasopressin, used to treat diabetes, and oxytocin that is able to act as hormone and neurotransmitter.⁴ The S–S bond in these compounds helps improving their pharmacological activities. The disulfide bond is also present in several bioactive natural products, especially from marine origin.^{2,5} Diaryl disulfides also show interesting properties and some examples are shown in Figure 1. For instance, bis(2(acylamino)phenyl) disulfide **1** was found to be a novel inhibitor of cholesteryl ester transfer protein, which is an enzyme involved in atherosclerosis.⁶ 2,2'-Disulfanediylidibenzamide **2** showed antibacterial activity against *Bacillus cereus*,⁷ whereas diamide disulfide **3** and its copper complex showed bacteriostatic activity and DNA-binding properties.⁸ Macrocyclic disulfide **4** presented anti-HIV activity.⁹ Diaryl disulfide **5** was found to be a novel stabilizer of tumor suppressor Pcd4, inhibiting cellular proliferation.¹⁰ Triazolyl phenyl disulfide **6** showed a potential herbicidal effect against *Arabidopsis thaliana*, inhibiting the enzyme 8-amino-7-oxononanoate synthase, which is implicated in biotin biosynthesis.¹¹ Natural diaryl disulfides are also known, such as

compounds **7** and **8** from the lissoclibadin family, which possess antimicrobial activity,¹² and compound **9** from the lissoclinotoxin family, which shows anticancer activity.¹³ Bis(*o*-amino)disulfide **10** showed in vitro antibacterial activity against multidrug resistant *Acinetobacter baumannii*.¹⁴ This same compound has been reported to present a significant herbicidal activity on aquatic weeds.¹⁵

In this respect, the weed control has become a difficult task nowadays because of the phenomena of weed resistance to herbicides.¹⁶ Each year, new weed species has become resistant to the commonly used herbicides in agriculture,¹⁷ bringing significant economic losses. At the same time, with the advent of glyphosate-resistant crops, the efforts to discover new herbicides have dramatically decreased.¹⁸ Thus, the design of new and safer herbicides with new modes of action to circumvent this problem is of paramount importance.

In continuation of our search for molecules with potent phytotoxic activities and motivated by the already mentioned herbicidal activity of disulfide **10** on aquatic weeds, herein, we report our findings on symmetrical bis(*o*-amino)- and bis(*o*-

Received: November 19, 2018

Accepted: January 15, 2019

Published: January 30, 2019

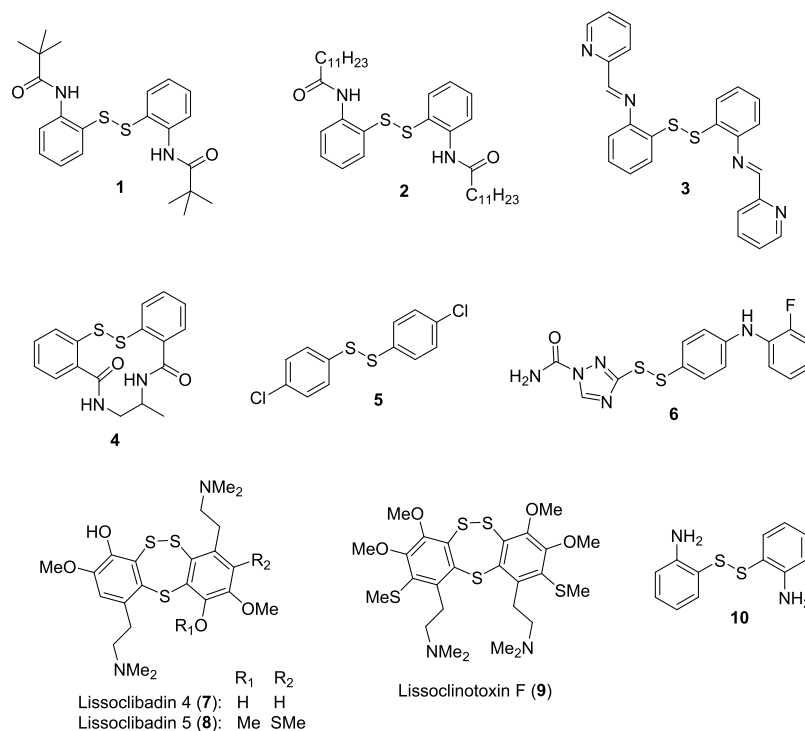


Figure 1. Diaryl disulfides with interesting properties.

Scheme 1. Synthesis of Compounds 10–15

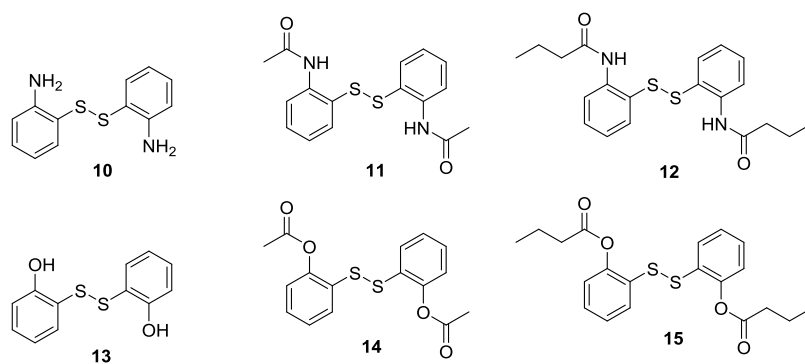
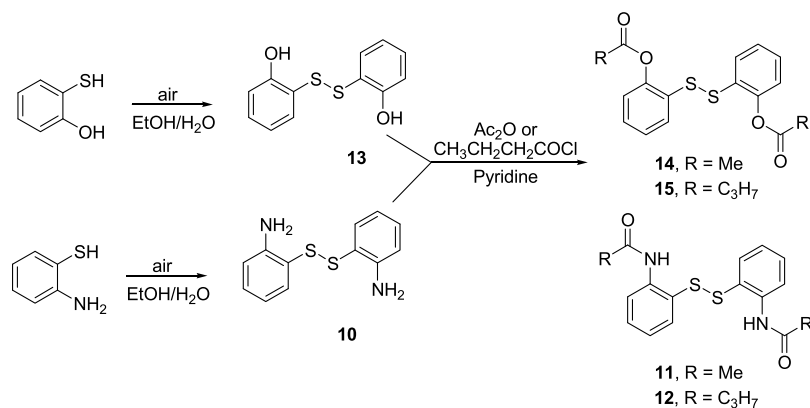


Figure 2. Compounds tested in this work.

hydroxy)phenyl disulfides and some of their acyl derivatives (compounds 10–15, Scheme 1, Figure 2). The phytotoxicity of these compounds was evaluated in two different types of bioassays: wheat coleoptile elongation and germination and

growth of different seeds. Coleoptile bioassays are widely used in the initial evaluation of phytotoxic activity,¹⁹ furnishing fast results (24 h) and good sensibility to bioactive molecules.^{20,21} The most active ones in this bioassay were tested in seeds of

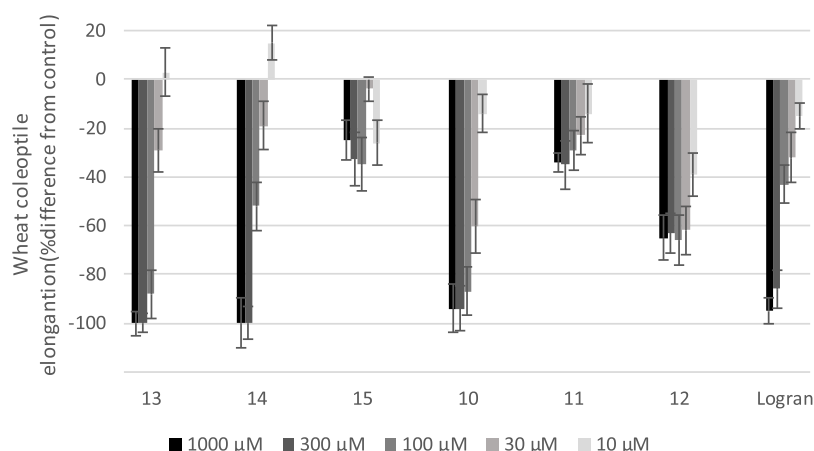


Figure 3. Effect of triasulfuron herbicide (Logran) and of disulfides **10**–**15** on wheat coleoptile elongation. Positive values indicating stimulation of growth vs the control and negative values indicating inhibition.

Table 1. IC_{50} (μM) and $A \log P$ Values for the Different Compounds Used in This Work

	compounds						Logran
	10	11	12	13	14	15	
IC_{50} (μM)	9.54	4228	1400	24.51	27.34	5022	39.5
R^2	0.9887	0.9492	0.8185	0.9797	0.9904	0.8944	0.9503
$\log IC_{50}$	0.979	3.626	3.146	1.389	1.437	3.701	1.596
$A \log P$	2.65	3.62	4.85	3.72	4.89	6.19	

four different types of plant species to evaluate their effects on the germination and plant growth. The first type of plant was tomato (*Solanum lycopersicum* L.—Solanaceae), a standard target species (STS) as a model for dicotyledonous species.²² This commercial crop seed is used in the phytotoxic assays for its homogeneous growth, good germination, and sensibility.²² The second type of plant evaluated was important weeds from the Poaceae family that greatly affect agriculture, such as ryegrass (*Lolium rigidum* Gaudin) and barnyard grass (*Echinochloa crus-galli* L.). These species directly affect important crops worldwide (mainly rice, cotton, corn, and potato), reducing the productivity, and the use of herbicides is necessary to control their incidence. Although the chemical control of these weeds is a common thing nowadays, these plants have shown resistance to the available herbicides, including glyphosate. The last type of evaluated plant was brachiaria (*Urochloa decumbens* (Stapf) R.D. Webster), an African grass with a high invasiveness potential because of its easy adaptation to different environments, besides being highly aggressive and resilient.²³ African grasses have been a subject of much concern because of their ability to invade natural environments, mainly in the Americas.²⁴ These characteristics make it strong enough to survive even under unfavorable conditions, causing problems of reduction of the biodiversity in natural environments, mainly in Brazilian savannas.²⁵

RESULTS AND DISCUSSION

The initial inhibitory activity of compounds **10**–**15** on wheat coleoptiles elongation is shown in Figure 3. The most active compounds with lower IC_{50} values than the commercial herbicide Logran (39.50 μM) used as a positive control were found to be **10** (9.54 μM), **13** (24.51 μM), and **14** (27.34 μM) (Table 1). Furthermore, **13** and **14** showed a remarkable activity (100% inhibition on the two highest concentrations) and compound **10** over 90% inhibition. Regarding compound

12 (IC_{50} 1400), it showed a moderate inhibition (65% on the highest concentrations) but its activity remains at lower concentrations. Analyzing the lipophilicity data of the compounds by their $\log P$ values²⁶ (Table 1), some trends were observed. For the oxygen-containing compounds **13**–**15**, the activity dropped drastically when a longer carbon chain was introduced and the more lipophilic compound **15** was the least active of all. Surprisingly, this direct relationship was not observed for the nitrogen-containing compounds **10**–**12**. This may be attributed to the very low solubility observed for compound **11** in buffered dimethyl sulfoxide. Thus, compounds **10**, **12**, **13**, and **14** were selected to be further evaluated in the phytotoxic activity on seed germination and growth bioassays. The results are shown in Figure 4.

All tested compounds caused a significant inhibition in the *S. lycopersicum* growth in at least one of the evaluated concentrations. Nevertheless, the inhibitory effects were distinct when compared within the compounds. Compounds **13** and **14** showed the highest inhibition on all growth parameters analyzed especially on the highest tested concentration (1000 μM , >90%), followed by compounds **10** and **12** with a moderate activity. Compound **14** showed a good dose–response relationship and superior activities were observed as compared to Logran. The higher effect of compounds **13** and **14** has also been observed on the germination in which around 80% inhibition was found on the highest tested concentration. In contrast, Logran did not show any significant activity. Interestingly, compound **12**, although with a low inhibition profile, was able to maintain its activity even after successive dilutions. The results obtained for *S. lycopersicum* (STS) indicate that this species is sensitive to the tested disulfides with remarkable results for compounds **13** and **14**.

Among the two weed crop species studied, better activities were observed on *L. rigidum*. Compounds **10** and **14** showed

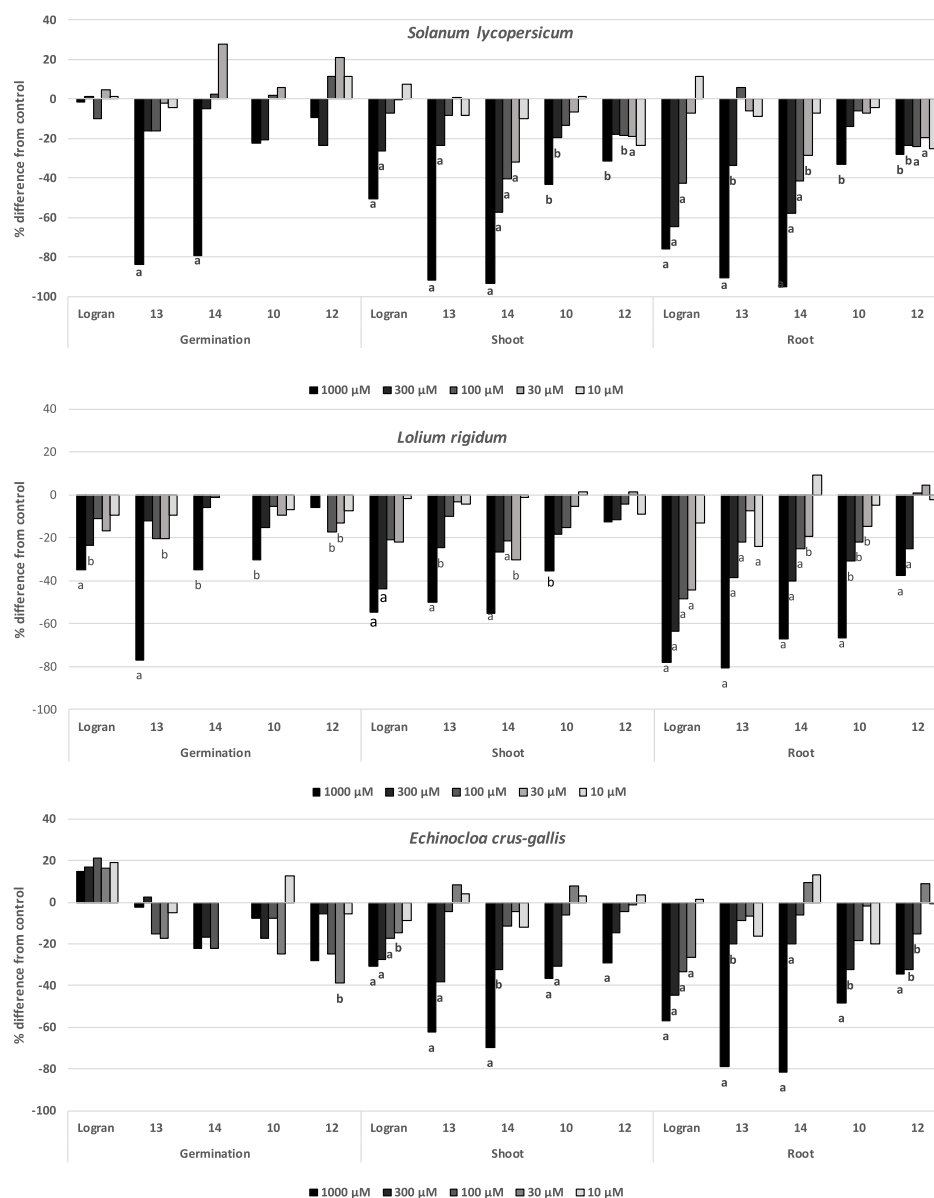


Figure 4. Effect of triasulfuron herbicide (Logran) and of disulfides 10, 12, 13, and 14 on germination and growth in different seeds. Values are expressed as percentage difference from control. Significance levels $p < 0.01$ (a) or $0.01 < p < 0.05$ (b). Positive values indicating stimulation of growth vs the control and negative values indicating inhibition.

very similar results whereas compound 13 was found to be the most active at the highest concentration. In the growth parameters, the roots were found to be more sensitive with a significant inhibition on all tested compounds. The effect on the shoot was significant only for compounds 13 and 14 with similar activities when compared to Logran. *L. rigidum* is a common weed in cereal crops and possesses a long history of resistance to the conventional herbicides.²⁷ The good inhibition presented by disulfides 10, 13, and 14 makes these compounds as potential candidates, which leads for the search of new herbicides for this weed crop control.

All tested compounds showed expressive inhibitory effect on the growth of *E. crus-galli*. The most significant effects were observed once more for compounds 13 and 14 with higher inhibitions in the highest concentrations (60–70% on the shoot and 80% on the root) as compared to Logran (30 and 60%, respectively). In contrast, no effect was observed on germination. *E. crus-galli* is the main weed of rice crops and the

first reports of its resistance to herbicides date back to the 1990s.^{28–30} Compounds that show a good inhibition profile over this species appear as a potential solution to the high economic losses in agriculture caused by this weed. Thus, disulfides 13 and 14 arise as candidates for lead compounds.

U. decumbens was the only weed species in which the tested compounds did not show a significant effect on the growth. The only effect observed was the stimulation of germination by these compounds under higher dilution conditions (hormesis effect) but with low significance. This effect has also been observed with glyphosate, stimulating plant growth even in different concentrations of this widely used herbicide.³¹ *U. decumbens* as a target species usually shows low sensibility to many compounds in phytotoxic bioassays.^{32,33} In this sense, the results shown here for *U. decumbens* may be due to the great intrinsic variability of its seeds and its resistance to phytotoxic compounds. Thus, the use of this species as a target

in the search for new phytotoxic compounds that are able to overcome its resistance is still a big challenge.

In summary, disulfides **13** and **14** showed the most significant activities both on wheat coleoptiles and on plant growth bioassays, being active against all plants studied except for *U. decumbens*. It has also been demonstrated that some variations in the structures of the disulfides lead to a lack of activity (for instance, converting the hydroxyl group of **13** into a butyrate in **15** or the amine group of **10** into an acetamide in **11**). Interestingly, the acylated compound **14** retained the activity of **13** and **12** retained the activity of **10** to some extent. There are not many similar compounds tested as herbicides. Compound **6**, which also shows a disulfide moiety, was tested on *A. thaliana*. It produced the death of plants with a foliar treatment of 4 kg ha⁻¹.¹¹ **6** showed an inhibitory effect on the 8-amino-7-oxononanoate synthase. Studies are currently under way (for instance, substitution at the aromatic rings) in order to better understand the structure–activity relationship of these compounds and to find more promising compounds on this series.

MATERIALS AND METHODS

General. Nuclear magnetic resonance (NMR) spectra were obtained on a 500 spectrometer (Agilent, INOVA 500). Chemical shifts are given in ppm with respect to residual ¹H signals of CDCl₃ (δ 7.26) and ¹³C signals are referenced to the solvent signal (δ 77.0). The following abbreviations were used: s (singlet), d (doublet), t (triplet), m (multiplet), br (broad), dd (double doublet), td (triple doublet), and st (sextet). High-resolution mass spectrometry was performed on a SYNAPT G2 UPLC-QTOF ESI mass spectrometer (Waters, Milford, MA, USA). An ultrasonic bath (360 W, JP Selecta, Barcelona, Spain) was used to help in the solubilization of the samples, when necessary. Column chromatography was carried out on silica gel 0.060–0.200, 60A (Acros Organics, Geel, Belgium). Aluminum sheets coated with silica gel 60 F₂₅₄ and 60 RP-18 F_{254s} (Merck, Darmstadt, Germany) were used for thin-layer chromatography. Compounds were viewed under UV₂₅₄ light followed by spraying the plates with H₂SO₄/H₂O/HOAc (4:16:80, v/v/v) and heating at 80 °C. Acetone, ethyl acetate, dichloromethane, ethanol, and *n*-hexane for synthesis, extraction, column chromatography, and thin-layer chromatography were obtained from VWR Chemicals. Deuteriochloroform (deuteration degree of 99.8%) for NMR spectroscopy was obtained from VWR Chemicals. NaIO₃, 2-aminothiophenol, 2-mercaptophenol, acetic anhydride, and pyridine were obtained from Sigma-Aldrich and used as received. IC₅₀ values (Table 1) were fitted to a sigmoidal dose–response model for bioactivity using the GraphPad Prism v.5.00 software package.³⁴ The *A* log *P* values were obtained using the ALOPS v. 2.1 software.³⁵

Synthesis of Compounds. 2,2′-Disulfanediyldianiline (**10**). Compound **10** was prepared in 80% yield by air oxidation of 2-aminothiophenol (1.25 g, 10.0 mmol) in ethanol/water (15/15 mL) following the procedure previously described by Coelho and Campo.³⁶

N,N'-(Disulfanediyldibis(2,1-phenylene))diacetamide (**11**) and *N,N'*-(Disulfanediyldibis(2,1-phenylene))dibutyramide (**12**). To 40 mg (0.16 mmol) of **10** in 110 μ L of pyridine, an excess (3:1, 46 μ L) of acetic anhydride was added. It was further stirred at room temperature for 12 h. After this, 3 mL of AcOEt was added and compound **11** was precipitated. The solvent was decanted. The solid was washed with small

portions of EtOAc and dried in vacuum, affording **11** (40 mg, 0.12 mmol) in 75% yield, with no need of chromatographic purification. Spectroscopical data match with those recently reported.³⁷

This procedure was used to obtain **12** in 70% yield by reaction of **10** (50 mg, 0.20 mmol) with butyryl chloride (62 μ L, 0.60 mmol) and pyridine (140 μ L). ¹H NMR (CDCl₃, 500 MHz): 8.39 (d, *J* = 8.1 Hz, 2H), 7.96 (br s, 2H), 7.41–7.36 (m, 4H), 6.99 (td, *J* = 7.7 Hz, 1.2, 2H), 2.13 (t, *J* = 7.5 Hz, 4H), 1.64 (st, *J* = 7.5 Hz, 2H), 0.96 (t, *J* = 7.5 Hz, 6H), 2.57 (t, *J* = 7.4 Hz, 4H), 1.82 (st, *J* = 7.4 Hz, 2H), 1.06 (t, *J* = 7.4 Hz, 6H). ¹³C NMR (CDCl₃, 125 MHz): 171.2, 139.8, 136.4, 132.1, 124.1, 123.4, 120.9, 39.6, 18.8, 13.7. Negative-ion HRTOFMSSES[−] *m/z*: 333.0263 [*M* − *H*]⁺ (calcd for [*M* − *H*]⁺, 333.0255).

2,2′-Disulfanediyldiphenol (**13**). To a solution of 2-mercaptophenol (900 mg, 7.1 mmol) in acetone (35 mL), 60 mL NaIO₃ (1.41 g, 7.1 mmol) aqueous solution was added. The mixture was stirred for 12 h at room temperature. The mixture was extracted with Et₂O (5 \times). The organic phase was dried over anhydrous NaSO₄, and the solvent was removed to obtain compound **13** (877 mg, 7.1 mmol), in quantitative yield, with no need of further purification. Its spectroscopic data match with those previously described for this compound.³⁸

Disulfanediyldibis(2,1-phenylene)diacetate (**14**) and Disulfanediyldibis(2,1-phenylene)dibutyrate (**15**). To 50 mg (0.20 mmol) of **13** in 140 μ L of pyridine, an excess (3:1, 57 μ L) of acetic anhydride was added. It was further stirred at room temperature for 12 h. After this, 35 mL of EtOAc was added and the mixture was washed with a saturated solution of CuSO₄. The organic phase was dried over anhydrous Na₂SO₄ and evaporated to obtain 66 mg of a solid. This was subjected to column chromatography using silica gel as the stationary phase and eluted with hexane/EtOAc (4:1) to afford **14** (55 mg, 0.16 mmol) in 80% yield. ¹H NMR (CDCl₃, 500 MHz): 7.57 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.28 (td, *J* = 7.8, 1.6 Hz, 2H), 7.19 (td, *J* = 7.8, 1.4 Hz, 2H), 7.08 (dd, *J* = 7.8, 1.4 Hz, 2H), 2.31 (s, 6H). ¹³C NMR (CDCl₃, 125 MHz): 168.8, 148.7, 130.0, 129.1, 126.8, 122.8, 20.7. Positive-ion HRTOFMSSES⁺ *m/z*: 391.1042 [*M* + *H*]⁺ (calcd for [*M* + *H*]⁺, 391.1038).

This procedure was used to obtain **15** in 87% yield by reaction of **13** (50 mg, 0.20 mmol) with butyryl chloride (62 μ L, 0.60 mmol) and pyridine (140 μ L). **15** was isolated from the mixture using hexane/EtOAc (9:1) as the eluent. ¹H NMR (CDCl₃, 500 MHz): 7.57 (dd, *J* = 7.9, 1.6 Hz, 2H), 7.27 (td, *J* = 7.6, 1.6 Hz, 2H), 7.19 (td, *J* = 7.6, 1.3 Hz, 2H), 7.08 (dd, *J* = 7.9, 1.3 Hz, 2H), 2.57 (t, *J* = 7.4 Hz, 4H), 1.82 (st, *J* = 7.4 Hz, 2H), 1.06 (t, *J* = 7.4 Hz, 6H). ¹³C NMR (CDCl₃, 125 MHz): 171.5, 148.6, 129.7, 129.1, 128.5, 126.7, 122.7, 36.0, 18.4, 13.7. Negative-ion HRTOFMSSES[−] *m/z*: 387.1207 [*M* − *H*]⁺ (calcd for [*M* + *H*]⁺, 387.1201).

Wheat Coleoptile Bioassay and Bioassay on Tomato and Weed Seeds. Wheat coleoptile bioassays as well as seed bioassays were performed according to procedures already described by our group.³⁹ Compounds **10**–**15** were tested on the wheat coleoptile bioassay from 1000 to 10 μ M (3 replicates) using Logran solutions at the same concentrations as the positive control. This pre- and postemergence herbicide is a combination of terbutryn and tiosulfuron and was previously selected for phytotoxicity bioassays based on the most consistent profile of activity. Any compound with equal or higher activity than the internal standard should be

considered as a potential new herbicide model.²² Data were statistical analyzed using Welch's test⁴⁰ and are presented as percent difference from the negative control (solution without any compound). Therefore, negative values mean inhibition of the studied parameter and positive values mean stimulation. IC₅₀ values were obtained by adjusting the effect data to the logarithm of concentration to a sigmoidal dose–response curve with the equation

$$Y = Y_{\min} + \frac{Y_{\max} - Y_{\min}}{1 + 10^{\log \text{EC}_{50} - X}}$$

Compounds **10**, **12**, **13**, and **14** were selected for the bioassay on seeds. They were tested on *Solanum lycopersicum* L., *L. rigidum* Gaudin, *E. crus-galli* (L.) Beauvois, and *U. decumbens* (Stapf) R. D. Webster, from 1000 to 10 μM (4 replicates) using Logran solutions at the same concentrations. Parameters were measured using the Fitomed system⁴¹ and statistically analysed by the use of the associated software using Welch's test. Significance was fixed at 0.01 and 0.05.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This research was supported by the Ministerio de Economía, Industria y Competitividad (MINEICO) (project AGL2017-88-083-R). S.C.C.O. and C.K.Z.A. acknowledge financial support from Universidade de Brasília, Brazil.

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